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=> d his

     (FILE 'HOME' ENTERED AT 15:02:41 ON 31 JUL 2003)

     FILE 'REGISTRY' ENTERED AT 15:02:51 ON 31 JUL 2003
                E ESTRADIOL/CN
                E 17 ESTRADIOL/CN

     FILE 'CAPLUS' ENTERED AT 15:06:31 ON 31 JUL 2003

     FILE 'REGISTRY' ENTERED AT 15:06:44 ON 31 JUL 2003
                E 17 ESTRADIOL/CN

     FILE 'CAPLUS' ENTERED AT 15:06:44 ON 31 JUL 2003

     FILE 'REGISTRY' ENTERED AT 15:07:03 ON 31 JUL 2003
                E ESTRADIOL/CN
L1              1 S E3

     FILE 'REGISTRY' ENTERED AT 15:08:17 ON 31 JUL 2003
L2              1 S 50-28-2/RN
                  SET NOTICE 1 DISPLAY
                  SET NOTICE LOGIN DISPLAY

     FILE 'REGISTRY' ENTERED AT 15:08:41 ON 31 JUL 2003
                SET TERMSET E#
                DEL SEL Y
                SEL L2 1 RN
L3              1 S E1/RN
                  SET TERMSET LOGIN

     FILE 'USPATFULL' ENTERED AT 15:08:44 ON 31 JUL 2003
L4            998 S L3
L5             30 S L4 AND PY<=1999 AND (HYPERCHOLEST? OR HYPERLIPID? OR LDL OR H
L6             27 S L5 AND ESTRADIOL

     FILE 'REGISTRY' ENTERED AT 15:17:13 ON 31 JUL 2003
                SET TERMSET E#
                DEL SEL Y
                SEL L2 1 RN
L7              1 S E1/RN
                  SET TERMSET LOGIN

     FILE 'CAPLUS' ENTERED AT 15:17:19 ON 31 JUL 2003
L8          49282 S L7
L9            384 S L8 AND PY<=1999 AND (HYPERCHOLEST? OR HYPERLIPID? OR LDL OR H
L10           376 S L9 AND ESTRADIOL
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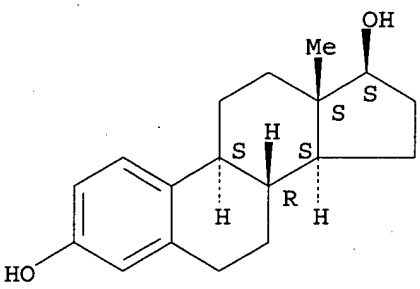
L1 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2003 ACS on STN
RN 50-28-2 REGISTRY

Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

CN Estra-1,3,5(10)-triene-3,17-diol (17.beta.)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN **Estradiol (8CI)**
OTHER NAMES:
CN (+)-3,17.beta.-Estradiol
CN .beta.-Estradiol
CN 13.beta.-Methyl-1,3,5(10)-gonatriene-3,17.beta.-ol
CN 17.beta.-Estradiol
CN 17.beta.-Oestradiol
CN 3,17-Epidihydroxyestratriene
CN 3,17.beta.-Dihydroxyestra-1,3,5(10)-triene
CN 3,17.beta.-Estradiol
CN Aerodiol
CN Altrad
CN Aquadiol
CN Bardiol
CN Beta-estradiol
CN Climaderm
CN Climara
CN Compudose
CN Compudose 200
CN Compudose 365
CN Corpagen
CN Dermestril
CN Dihydrofollicular hormone
CN Dihydrofolliculin
CN Dihydromenformon
CN Dihydrotheelin
CN Dihydroxyestrin
CN Dimenformon
CN Diogyn
CN Diogynets
CN Divigel
CN E 2
CN Encore
CN Epiestriol 50
CN Estra-1,3,5(10)-triene-3,17-diol, (17.beta.)-
CN Estra-1,3,5(10)-triene-3,17.beta.-diol
CN Estrace
CN Estraderm
CN Estraderm TTS
CN Estraderm TTS 100

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25

CN Estraderm TTS 50
CN Estradot
CN Estraldine
CN Estring Vaginal Ring
CN Estroclim
CN Estroclim 50
CN Estrogel
CN Estrovite
CN Evorel
CN Femestral
CN Femogen
ADDITIONAL NAMES NOT AVAILABLE IN THIS FORMAT - Use FCN, FIDE, or ALL for DISPLAY

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     (FILE 'HOME' ENTERED AT 11:55:45 ON 31 JUL 2003)

     FILE 'EUROPATFULL, PATDPAFULL, PCTFULL, RDISCLOSURE, USPATFULL, USPAT2,
     WPIDS' ENTERED AT 11:59:20 ON 31 JUL 2003
L1          8332 S ESTROGEN(S)(ANTIESTROGEN OR (ESTROGEN(3A)RECEPTOR))
L2           478 S L1(S)(DHEA OR DEHYDROEPIANDROSTERONE OR BISPHOSPHONATE#)
L3           106 S L1(S)(DHEA OR DEHYDROEPIANDROSTERONE)
L4            25 S L3 NOT PY>=1999
L5             7 S L3(S)(CHOLESTEROL OR LDL OR HYPERLIPID? OR HYPERCHOLESTER?)
L6             2 S L5 NOT PY>=2000
```

L6 ANSWER 2 OF 2 PCTFULL COPYRIGHT 2003 Univentio on STN
ACCESSION NUMBER: 1999063974 PCTFULL ED 20020515
TITLE (ENGLISH): MEDICAL USES OF A SELECTIVE ESTROGEN RECEPTOR MODULATOR IN COMBINATION WITH SEX STEROID PRECURSORS
TITLE (FRENCH): UTILISATIONS MEDICALES D'UN MODULATEUR DE RECEPTEUR D'OESTROGENES SELECTIF EN ASSOCIATION AVEC DES PRECURSEURS DE STEROIDES SEXUELS
INVENTOR(S): LABRIE, Fernand
PATENT ASSIGNEE(S): ENDORECHERCHE, INC.
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 9963974	A2	19991216

DESIGNATED STATES
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG UZ VN YU ZA ZW GH GM KE LS MW SD SL SZ UG ZW AM AZ BY KG KZ MD RU TJ TM AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE BF BJ CF CG CI CM GA GN GW ML MR NE SN TD TG
APPLICATION INFO.: WO 1999-CA538 A 19990610
PRIORITY INFO.: US 1998-09/096,284 19980611

ABEN Novel methods for the medical treatment and/or inhibition of the development of osteoporosis, breast cancer, **hypercholesterolemia**, **hyperlipidemia** or atherosclerosis in susceptible warm-blooded animals including humans involving administration of selective **estrogen receptor** modulator particularly compounds having general structure (I) and an amount of a sex steroid precursor selected from the group consisting of **dehydroepiandrosterone**, **dehydroepiandrosterone** sulfate, androst-5-ene-3β,17β-diol and compounds converted i(in vivo) to one of the foregoing precursor. Further administration of bisphosphonates in combination with selective **estrogen receptor** modulators and/or sex steroid precursor is disclosed for the medical treatment and/or inhibition of the development of osteoporosis. Pharmaceutical compositions. . .

DETD MEDICAL USES OF A SELECTWE **ESTROGEN RECEPTOR** MODULATOR IN
COMBINATION WITH SEX STEROID PRECURSORS
FIELD OF THE INVENTION
The present invention relates to a method for treating or reducing the likelihoocl or' acquiring osteoporosis, hy percholesterolen-da, **hyperlipidemia** or atherosclerosis usina a novel combination therapy on susceptible warm-blooded animals, including humam. In particular, the combination includes administering a selective **estrogen receptor** modulator (SERN4) and raising the patient's level of precursor to sex steroids, said precursor beinor selected from the group consistirig of **dehydroepiandrosterone** (I)HEA), **dehydroepiandrosterone** sulfate (I)FEA-S), and androst ene-3p,17p-diol (57diol). The invention also relates to kits and pharmaceutical composition for practicing the foregoing combination.

In another ernbodiment, the invention provides a method of treating or reducing the risk
of acquiring **hypercholesterolen**-da comprising increasing
levels of a sex steroid precursor
selected from the group consisting of **dehydroepiandrosterone**,
dehydroepiandrosterone-
sulfate and androst ene-3p,17[@-diol , in a patient in need of said treatment or said
reduction, and further comprising administering to said patient a therapeutically effective
amount of a selective **estrogen receptor** modulator as
part of a combination therapy.

CLMEN 1 A method of treating or reducing the risk of acquiring a
condition selected from the group consisting of osteoporosis,
hypercholesterolen-da, hy erlipidemia, atherosclerosis, breast cancer,
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endornetrial cancer, uterine cancer, ovarian cancer, vaginal dryness and loss of muscle mass, said method comprising increasing levels of a sex steroid precursor selected from the group consisting of
dehydroepiandrosterone, **dehydroepiandrosterone**
sulfate, androst
ene-30,17p-diol and 4-androsten-3,17-dione in a patient in need of said treatment or said reduction, and further comprising administering to said patient a therapeutically effective amount of a selective
estrogen
receptor modulator as part of a combination therapy.

L4 ANSWER 18 OF 25 USPATFULL on STN
ACCESSION NUMBER: 97:94225 USPATFULL
TITLE: Derivatives of estra 1,3,5(10)triene-17-one,3-amino compounds and their use
INVENTOR(S): Li, Pui-Kai, Library, PA, United States
Selcer, Kyle W., Export, PA, United States
PATENT ASSIGNEE(S): Duquesne University of the Holy Ghost, Pittsburgh, PA, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5677292		19971014
APPLICATION INFO.:	US 1996-607797		19960227 (8)

RELATED APPLN. INFO.: Division of Ser. No. US 1994-341410, filed on 17 Nov 1994
DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Reamer, James H.
LEGAL REPRESENTATIVE: Eckert Seamans Cherin & Mellott
NUMBER OF CLAIMS: 38
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 6 Drawing Figure(s); 4 Drawing Page(s)
LINE COUNT: 1007
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
DETD The present invention deals with using estra-1,3,5(10)triene-17-one, 3 amino derivatives and the respective **dehydroepiandrosterone** and pregnenolone derivatives as estrone sulfatase inhibitors. Little is known about the metabolism of these compounds and the possible effects. . . metabolite of the estra 1,3,5(10)triene-17-one derivative is estra-1,3,5(10)-triene-17-one, 3-amine (E.sub.1 -NH.sub.2). The procedure and results of the estrogenicity, anti-estrogenicity and **estrogen receptor** binding affinity of E.sub.1 NH.sub.2 are shown below.

L4 ANSWER 19 OF 25 USPATFULL on STN
ACCESSION NUMBER: 97:20519 USPATFULL
TITLE: Method of treatment of androgen-related diseases
INVENTOR(S): Labrie, Fernand, Ste-Foy, Canada
PATENT ASSIGNEE(S): Endorecherche Inc., Canada (non-U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5610150		19970311
APPLICATION INFO.:	US 1995-472512		19950607 (8)

RELATED APPLN. INFO.: Division of Ser. No. US 1993-98607, filed on 10 Sep 1993 which is a division of Ser. No. US 1992-963278, filed on 19 Oct 1992, now patented, Pat. No. US 5372996 which is a continuation of Ser. No. US 1989-376710, filed on 7 Jul 1989, now abandoned
DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Jordan, Charles T.
ASSISTANT EXAMINER: Chi, Anthony R.
LEGAL REPRESENTATIVE: Ostrolenk, Faber, Gerb & Soffen, LLP
NUMBER OF CLAIMS: 15
EXEMPLARY CLAIM: 9
NUMBER OF DRAWINGS: 1 Drawing Figure(s); 1 Drawing Page(s)
LINE COUNT: 1639
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
SUMM . . . a schematic representation of the site(s) of action of various drugs, enzymes and hormones. The following abbreviations are used: ER: **estrogen receptor**; AR: androgen **receptor**; **DHEA**: **dehydroepiandrosterone**; .DELTA..sup.5 -diol:

androst-5-ene-3 .beta., 17.beta.-diol; .DELTA..sup.4 -dione: androstenedione; DHT: dihydrotestosterone; Anti-A: antiandrogen; Anti-E **antiestrogen**; ARO: aromatase; 3.beta.-HSD: 3.beta.-hydroxysteroid dehydrogenase, .DELTA..sup.5 -.DELTA..sup.4 isomerase; 17.beta.-HSD: 17.beta.-hydroxysteroid dehydrogenase; 1: antiandrogen; 17.beta.-hydroxysteroid dehydrogenase activity; 4: **antiestrogen** ; 5; inhibitor of aromatase activity; 6: inhibitor of 3.beta.-HSD activity.

SUMM . . . androgen receptor is shown to stimulate prostatic cancer growth, and is therefore to be prevented. In addition, stimulation of the **estrogen receptor** leads to increased levels of androgen receptors and thus may, in addition, exert direct stimulatory effects on prostatic cancer growth. The action of **estrogens** is therefore to be prevented. Blockers of sex steroid formation from **DHEA** and .DELTA..sup.4 -dione in peripheral tissues does not cause inhibition of adrenal glucocorticoid formation. For example, cortisol and aldosterone production. . . result from their inhibition are avoided. The desired inhibition of sex steroid formation is thus aimed selectively at androgens and **estrogens**.

L4 ANSWER 20 OF 25 USPATFULL on STN

ACCESSION NUMBER:	97:5964 USPATFULL
TITLE:	Combination therapy for prophylaxis and/or treatment of benign prostatic hyperplasia
INVENTOR(S):	Labrie, Fernand, Ste-Foy, Canada
PATENT ASSIGNEE(S):	Endorecherche Inc., Quebec, Canada (non-U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5595985		19970121
APPLICATION INFO.:	US 1993-167450		19931215 (8)

RELATED APPLN. INFO.: Continuation of Ser. No. US 1992-925883, filed on 6 Aug 1992, now abandoned which is a continuation of Ser. No. US 1989-376700, filed on 7 Jul 1989, now abandoned which is a continuation-in-part of Ser. No. US 1989-322154, filed on 10 Mar 1989, now abandoned

DOCUMENT TYPE:	Utility
FILE SEGMENT:	Granted
PRIMARY EXAMINER:	Kishore, Gollamudi S.
LEGAL REPRESENTATIVE:	Ostrolenk, Faber, Gerb & Soffen, LLP
NUMBER OF CLAIMS:	7
EXEMPLARY CLAIM:	1
NUMBER OF DRAWINGS:	1 Drawing Figure(s); 1 Drawing Page(s)
LINE COUNT:	1427

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

DRWD . . . of action of drugs active in the prophylaxis and/or treatment of benign prostatic hyperplasia (BPH). The following abbreviations are used: **DHEA**, **dehydroepiandrosterone**; .DELTA..sup.5 -diol, androst-5-ene-3.beta., 17.beta.-diol; .DELTA..sup.4 -dione, androstenedione; T, testosterone; DHT, dihydrotestosterone; E.sub.1, estrone; E.sub.2, 17.beta.-estradiol; ER, **estrogen receptor**; anti-E, **antiestrogen** (2); anti-A, anti-androgen (5); 17.beta.-HSD, inhibitor of 17.beta.-hydroxysteroid dehydrogenase (4); 3.beta.-HSD, inhibitor of 3.beta.-hydroxysteroid dehydrogenase, .DELTA..sup.5 -.DELTA..sup.4 - isomerase (6),. . .

L10 ANSWER 6 OF 376 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1999:765006 CAPLUS
DOCUMENT NUMBER: 131:346787
TITLE: Double-blind randomized placebo-controlled study of transdermal estrogen replacement therapy on hypertensive postmenopausal women
AUTHOR(S): Modena, Maria Grazia; Molinari, Rosella; Muia, Nicola, Jr.; Castelli, Annadele; Pala, Francesca; Rossi, Rosario
CORPORATE SOURCE: Institute of Cardiology II, Department of Internal Medicine, Policlinico Hospital, University of Modena, Modena, Italy
SOURCE: American Journal of Hypertension (**1999**), 12(10, Pt. 1), 1000-1008
CODEN: AJHYE6; ISSN: 0895-7061
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB We investigated the effects of transdermal 17.beta.-**estradiol**, combined with std. antihypertensive therapy, on the modification of the cardiovascular risk profile in hypertensive postmenopausal women. In a randomized, double-blind, placebo-controlled study, we enrolled 200 postmenopausal women with mild to moderate hypertension. Patients received 17.beta.-**estradiol** (50 .mu.g/day, transdermal) and norethisterone acetate (2.5 mg/day, orally) or placebo. At baseline serum total cholesterol, **LDL** cholesterol, **HDL** cholesterol, triglycerides, glucose, and fibrinogen plasma levels were measured and all subjects underwent complete M-mode and 2-D endocardiograms, which were repeated after 6, 12, and 18 mo of hormonal replacement therapy. Compared with placebo, all values decreased significantly except for **HDL** cholesterol. In both groups, no modifications were obsd. in echocardiog. parameters, except for left ventricular mean diastolic and systolic wall thickness and left ventricular mass index, which showed a significant decrease in both groups. The redn. was greater in the treated group; the percentage of patients with left ventricular hypertrophy was 46% before randomization and 17.2% after 18 mo of treatment (P <.0001), whereas in group II the percentage was 48% at baseline and 31.5% after 18 mo (P <.05). In conclusion, transdermal 17.beta.-**estradiol**, assocd. with antihypertensive therapy, may contribute to the redn. of cardiovascular risk profile in hypertensive postmenopausal women.
REFERENCE COUNT: 61 THERE ARE 61 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

10/052,803

L10 ANSWER 25 OF 376 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1999:341400 CAPLUS
DOCUMENT NUMBER: 131:97765
TITLE: Effect of 17.beta.-**estradiol** in **hypercholesterolemic** rabbits with severe endothelial dysfunction
AUTHOR(S): Do Nascimento, Carlos Antonio; Kauser, Katalin; Rubanyi, Gabor M.
CORPORATE SOURCE: University of Sao Paulo, Sao Paulo, 01246-903, Brazil
SOURCE: American Journal of Physiology (**1999**), 276(5, Pt. 2), H1788-H1794
CODEN: AJPHAP; ISSN: 0002-9513
PUBLISHER: American Physiological Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB 17.beta.-**Estradiol** prevents early vascular lesion development and may also affect advanced atherosclerosis. To test the antiatherosclerotic effect of estrogen under conditions that resemble more advanced human atherosclerosis with severe endothelial dysfunction, we have investigated the effect of 17.beta.-**estradiol** in **hypercholesterolemic** rabbits treated with the nitric oxide synthase inhibitor N.omega.-nitro-L-arginine Me ester (L-NAME). Chronic L-NAME administration attenuated endothelial nitric oxide (EDNO)-mediated vascular responses leading to significantly accelerated atherosclerotic plaque development. 17.beta.-**Estradiol** treatment alone inhibited aortic lesion formation with concurrent increase in EDNO-mediated responses. The beneficial effect of estrogen persisted in the L-NAME-treated rabbits, suggesting that the antiatherogenic action of 17.beta.-**estradiol** involves NO-independent mechanisms as well. Serum cholesterol levels were not altered by any of the treatments. 17.beta.-**Estradiol** treatment significantly increased EDNO prodn. under these conditions as well. The redn. in plaque size by 17.beta.-**estradiol** was always accompanied by increased EDNO prodn., suggesting a strong assocn. between these two events. The results demonstrate that estrogen treatment may exert protection against atherosclerosis even in patients with severe endothelial dysfunction.

REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

TI Effect of 17.beta.-**estradiol** in **hypercholesterolemic** rabbits with severe endothelial dysfunction
SO American Journal of Physiology (**1999**), 276(5, Pt. 2), H1788-H1794
CODEN: AJPHAP; ISSN: 0002-9513

AB 17.beta.-**Estradiol** prevents early vascular lesion development and may also affect advanced atherosclerosis. To test the antiatherosclerotic effect of estrogen under conditions that resemble more advanced human atherosclerosis with severe endothelial dysfunction, we have investigated the effect of 17.beta.-**estradiol** in **hypercholesterolemic** rabbits treated with the nitric oxide synthase inhibitor N.omega.-nitro-L-arginine Me ester (L-NAME). Chronic L-NAME administration attenuated endothelial nitric oxide (EDNO)-mediated vascular responses leading to significantly accelerated atherosclerotic plaque development. 17.beta.-**Estradiol** treatment alone inhibited aortic lesion formation with concurrent increase in EDNO-mediated responses. The beneficial effect of estrogen persisted in the L-NAME-treated rabbits, suggesting that the antiatherogenic action of 17.beta.-**estradiol** involves NO-independent mechanisms as well. Serum cholesterol levels were not altered by any of the treatments. 17.beta.-**Estradiol** treatment significantly increased EDNO prodn. under these conditions as well. The redn. in plaque size by 17.beta.-**estradiol** was always accompanied by increased EDNO prodn., suggesting a strong assocn. between these two events. The results demonstrate that estrogen treatment may exert protection against

atherosclerosis even in patients with severe endothelial dysfunction.

ST **estradiol** endothelium dysfunction **hypercholesterolemia** ; antiatherosclerotic **estradiol** nitric oxide

IT **Hypercholesterolemia**
(17.beta.-**estradiol** protection against atherosclerosis in **hypercholesterolemic** rabbits with severe endothelial dysfunction and nitric oxide role therein)

IT Antiarteriosclerotics
(antiatherosclerotics; 17.beta.-**estradiol** protection against atherosclerosis in **hypercholesterolemic** rabbits with severe endothelial dysfunction and nitric oxide role therein)

IT 10102-43-9, Nitric oxide, biological studies
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative); PROC (Process)
(17.beta.-**estradiol** protection against atherosclerosis in **hypercholesterolemic** rabbits with severe endothelial dysfunction and nitric oxide role therein)

IT **50-28-2**, 17.beta.-**Estradiol**, biological studies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(17.beta.-**estradiol** protection against atherosclerosis in **hypercholesterolemic** rabbits with severe endothelial dysfunction and nitric oxide role therein)

IT 57-88-5, Cholesterol, biological studies
RL: BOC (Biological occurrence); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence)
(17.beta.-**estradiol** protection against atherosclerosis in **hypercholesterolemic** rabbits with severe endothelial dysfunction and nitric oxide role therein)

IT 57-88-5, Cholest-5-en-3-ol (3.beta.)-, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(blood; 17.beta.-**estradiol** protection against atherosclerosis in **hypercholesterolemic** rabbits with severe endothelial dysfunction and nitric oxide role therein)